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Original Research

Evaluating inflammatory markers as predictive tools for advanced non-small cell lung cancer receiving nivolumab

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Abstract

Aim: Non-small cell lung cancer (NSCLC) is a significant cause of cancer-related morbidity and mortality worldwide. In recent years, immunotherapies such as Nivolumab have revolutionized treatment strategies, demonstrating enhanced survival and response profiles compared to traditional platinum-based therapies. This study elucidated the prognostic significance of pretreatment hematological parameters, including Neutrophil- Lymphocyte Ratio (NLR), Systemic Immune-Inflammation Index (SII), and Prognostic Nutritional Index (PNI), in NSCLC patients undergoing Nivolumab treatment.

Material and Methods: This retrospective study included patients treated with Nivolumab for pathologically proven advanced NSCLC between January 2019 and March 2021. Hemogram parameters and clinicopathological and clinicopathological factors before Nivolumab treatment were recorded from the hospital's electronic data record system. Survival analysis was conducted using the Kaplan-Meier method and the Log-Rank test was utilized for comparison. Multivariate analysis of factors affecting survival was performed with the Cox proportional-hazards model.

Results: Ninety-two patients were included in this study. The median OS and PFS for all patients included in the analysis were 14.5 months and 11.1 months, respectively. The ideal cut-off value dividing NLR into 2 for overall survival time was calculated as 1.89 (AUC: 0.694, p=0.002) using Roc-Curve. In univariate analysis, ECOG performance score (p<0.001), leukocytes (p < 0.029), high neutrophil (p < 0.018) as well as NLR (p <0 .018) were found to be associated with worse overall survival. Multivariate Cox regression model demonstrated that ECOG (HR=3.54, 95% CI, 1.46-8.60, p =0.005) and NLR (HR=1.52, CI 1.16 - 2.01, p=.003) were significant predictors factors for survival.

Discussion: These results underline the critical role of inflammation and immune response in tumor progression and therapeutic outcomes. The identified markers offer a practical means of predicting patient responses to Nivolumab therapy, aiding in personalized treatment decisions. As NSCLC treatment paradigms shift towards immunotherapy, these easily accessible parameters could aid clinicians in selecting optimal therapeutic strategies for individual patients, ultimately contributing to improved clinical management and outcomes.

Keywords
Lung Cancer, Nivolumab, Overall Survival, Progression-Free Survival, NLR

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Introduction

Non-small cell lung cancer comprises approximately 85 percent of all lung cancers and is one of the significant causes of cancer-related mortality and morbidity worldwide [1]. Until about a decade ago, platinum-based doublet therapy was the standard in advanced lung cancer if a patient's cancer had no targetable driver mutation such as ALK, ROS, EGFR, etc. However, with the evolving and advancing treatment options, immunotherapy, and targeted therapies have gained priority in terms of both survival and side effect profiles. When the Checkmate 057 study presented its data in 2015, it showed that Nivolumab treatment improved overall survival compared to standard chemotherapy in patients having progressed after one line of platinum-based therapy, independent of Programmed death ligand-1 (PD-L1) [2]. Currently, immunotherapy treatment has an important impact on the frontline treatment management of NSCLC.

Immunotherapies have provided significant therapeutic potential in various cancer types where the immune response is effective. In particular, significant breakthroughs have been made with the help of emerging knowledge of the programmed death-1/programmed death ligand-1 (PD-1/PD-L1) pathway. PD-1 is a transmembrane protein expressed on T cells, B cells, and NK cells' surfaces and is an inhibitory molecule that binds to PD-L1. PD-1, PD-L1 interaction allows tumor survival by directly inhibiting tumor cell apoptosis, stimulating the transformation of T effector cells to Treg cells, and promoting peripheral T effector cell depletion [3.4.5]. Nivolumab is a novel human IgG4 immune checkpoint inhibitor antibody. It binds to PD-1 in the host and prevents its interaction with PD-L1 in the tumor cell [6,7]. By suppressing PD-1 function, nivolumab releases immune cells from pathological immune suppression and enables them to recognize and respond to tumor cells [8]. The high binding affinity and specificity of this interaction are responsible for a large extent of the clinical efficacy of antibodies as therapeutic molecules.

Inflammation, especially neutrophils, T-reg, and platelets in the tumor microenvironment, has been associated with tumor and disease progression [9]. The subject of the study was predictive markers according to which patients will receive maximum benefit from high-cost immunotherapies.

The aim of this study was to investigate the hemogram parameters, Neutrophil-Lymphocyte Ratio (NLR), Systemic Immune-Inflammation Index (SII), and Prognostic Nutritional Index (PNI) as well as clinicopathological factors as prognostic factors in terms of disease progression and survival.

Material and Methods

Patients

This retrospective study included patients who received Nivolumab treatment for pathologically proven advanced non-small cell lung cancer between January 2019 and March 2021. Inclusion criteria were as follows: patients who have progressed after at least one line of chemotherapy for metastatic disease, patients who relapsed within 6 months after chemotherapy for locally advanced disease, being over the age of 18 years, and have received at least 2 cycles of Nivolumab treatment. Patients with a history of concomitant or previous cancer disease, patients under 18 years of age, patients receiving concurrent chemotherapy or ipilimumab with Nivolumab, and patients whose data could not be obtained were excluded from the study.

Leukocytes, neutrophils, lymphocytes, hemoglobin, albumin, and CRP were obtained from peripheral blood samples before Nivolumab treatment, and clinicopathological data were recorded from the hospital's medical data record system. The Neutrophil-Lymphocyte Ratio (NLR) was calculated by dividing the baseline neutrophil count by the lymphocyte count; The Systemic Immune-Inflammation Index was determined by Platelet x NLR; the Prognostic Nutritional Index (PNI) was measured by the formula (10×serum albumin [g/dL])+(0.005×lymphocytes/μL). This study, conducted in accordance with the Declaration of Helsinki, was approved by the local Institutional Ethics Committee on 2021-27-04 with approval No: 2021.116.04.11.

Statistics

Statistical analysis was conducted using the Statistical Package for the Social Sciences version 25.0; SPSS Inc. Progression-free survival was accepted as the beginning time of Nivolumab treatment to any documented clinical progression, relapse, or death from any cause. The definition of overall survival (OS) was the time from the beginning of Nivolumab treatment until death from any cause. The Kaplan-Meier method was utilized for survival analysis and the Log-Rank test was employed for group comparison. Multivariate analysis of factors affecting survival was performed with the Cox proportional-hazards model. The "Forward: LR" method was used for multivariate analysis. Ideal cut-off values for laboratory parameters in OS or PFS analysis were established by Receiver Operating Characteristics. For other non-categorical variables, the median value was used as a cut-off. The statistical significance threshold was accepted as p=0.05.

Ethical Approval

Ethics Committee approval was obtained.

Results

Ninety-two consecutive patients were included in this study. Nine (9.8%) of all patients were female, 83 (90.2%) were male and the median age of the study population was 65 (47-84) years. Median OS and PFS for all patients included in the analysis were 14.5 months and 11.1 months, respectively. Fifty (54%) patients had the adenocarcinoma subtype and 42 (46%) patients had the squamous cell carcinoma subtype. Sixty-four patients received treatment as 2nd line treatment, while 28 patients received Nivolumab for later lines. The numbers of patients who progressed and died during the study period were 45 and 36, respectively. Clinical and laboratory characteristics of the patient population are summarised in Table 1.

Ideal Cut-off and ROC Curves

The ideal cut-off value for neutrophil-lymphocyte ratio in terms of progression-free survival time was found to be 1.89 by Roc-Curve (AUC: 0.679, p=0.003). For PFS, the ideal cut-off values for neutrophils and SII were 6550 103 /u (AUC: 0.635, p=0.026) and 419472 (AUC: 0.647, p=0.016), respectively.

The ideal cut-off value dividing NLR into 2 for overall survival time was calculated as 1.89 (AUC: 0.694, p=0.002) with Roc-Curve. The ideal cut-off values for leukocyte, neutrophil, and SII

were found as 6365 103 /u (AUC: 0.639, p=0.025), 6550 (AUC: 0.688, p= 0.002), 650430 (AUC: 0.655, p= 0.013), respectively.

Univariate and Multivariate Survival Analysis

In univariate analysis, ECOG performance score (p<0.001), high leucocytes (p<0.029), higher neutrophil (p<0.018) as well as high NLR (p<0.018) were significantly associated with poorer overall survival (Figure 1).

Tumor type, line of therapy, age, gender, body mass index, and PNI were not associated with survival (Table 2). In the multivariate Cox regression model, ECOG {Hazard Ratio (HR) = 3.54, 95% Confidence Interval (CI), 1.46 - 8.60, p = 0.005} and NLR (HR = 1.52, CI 1.16 - 2.01, p = 0.003) were found to be independent prognostic factors for survival (Table 3).

Table 1. Patient Characteristics.

Clinical Parameters		n	%
Age	< 65	50	54
	≥ 65	42	46
Sex	Female	9	9.8
	Male	83	90.2
ECOG PS	0-1	80	87
	≥ 2	12	13
Comorbidity	No	39	42.4
	Yes	53	57.6
Body-Mass Index	<25	57	62
	≥ 25	35	38
Tumor Type	Adenocarcinoma	50	54
	Squamous Cell Carcinoma	42	46
Treatment line for Nivolumab	Second line	64	69.6
	Later lines	28	30.4
ABO Blood Type	A / B / AB / 0	34/15/8/33	37/16.3/8.7/35.9
RH Blood Type	Negative / Positive	12.80	13/87

Laboratory Parameters	IQR(50th)	IQR(25th-75th)
White Blood Cell	7100	2400-7706
Neutrophil	4250	1210-5491
Lymphocyte	2275	1587-2845
Platelet Count	273000	207000-326000
Hemoglobin	11.38	10.11-12.37
CRP	17.5	6.88-50
Protein	6.99	6.59-7.36
Albumin	3.98	3.57-4.22
NLR	6.94	1.36-2.88
SII	473000	297565-837517
PNI	51.17	46.00-54.77

IQR: Inter Quartile Range, NLR: Neutrophil-Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index, PNI: Prognostic Nutritional Index

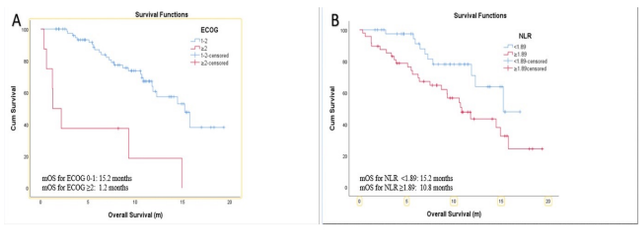

Figure 1. Kaplan-Meier plots of overall survival according to ECOG(A) and NLR (B).

Table 2. Kaplan-Meier analysis of patients' clinical and laboratory parameters.

Variables		n	PFS (m)	p	OS (m)	p
Age	< 65	50	9	0.424	14,5	0.314
	≥ 65	42	14		14,9	
Sex	Female	9	14.5	0.602	14,5	0.240
	Male	83	9.8		14,9	
ECOG PS	0-1	80	14.5	<0.001	15,2	<0.001
	≥ 2	12	1.3		1,3	
Comorbidity	No	39	9.8	0.777	12,3	0.806
	Yes	53	11.0		14,5	
Body-Mass Index	<25	57	9.3	0.293	11,8	0.063
	≥ 25	35	16.4		14	
Tumor Type	Adenocarcinoma	50	9.3	0.544	12,3	0.338
	Squamous Cell Carcinoma	42	11.0		15,2	
Treatment line for Nivolumab	Second line	64	9.8	0.606	12,3	0.431
	Later lines	28	14.5		14,5	
White Blood Cell	Low	39	14.9	0.196	14,7	0.029
	High	53	8.5		11,9	
Neutrophil	Low	46	14.9	<0.001	15,8	<0.001
	High	46	4.0		6,3	
Lymphocyte	Low	73	9.3	0.454	15,8	0.884
	High	19	14.0		14,5	
Platelet Count	Low	45	8.6	0.527	11,8	0.208
	High	47	14.0		15,8	
CRP	Low	46	11.0	0.360	15,2	0.249
	High	46	9.8		12,3	
NLR	Low	44	12.3	0.023	15,2	0.018
	High	48	9		10,8	
SII	Low	46	14.9	0.037	13,5	0.074
	High	46	8.6		11,2	
PNI	Low	46	8.6	0.079	11,8	0.374
	High	46	14.0		14,5	

ECOG PS: Eastern Cooperative Oncology Group Performance Status, NLR: Neutrophil-Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index, PNI: Prognostic Nutritional Index

Table 3. Multivariate Cox Regression Analyses of factors for PFS and OS.

		PFS		OS	
Variable	Category	HR (95% CI)	P f	HR (95% CI)	P f
NLR	<1.89 vs ≥1.89	3.39 (1.40- 8.20)	0.007	1.52 (1.16 - 2.01)	0.003
ECOG PS	0-1 vs ≥2	1.34 (1.06 – 1.67)	0.017	3.54 (1.46 - 8.60)	0.005

PFS: Progresion-Free Survival, OS: Overall Survival, NLR: Neutrophil-Lymphocyte Ratio, ECOG PS: Eastern Cooperative Oncology Group Performance Status

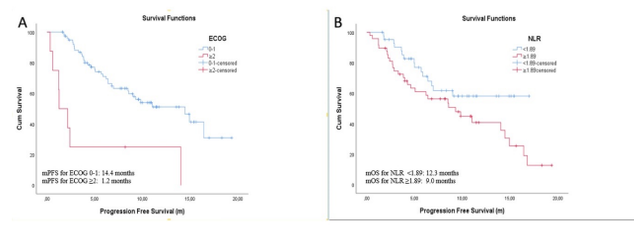

Figure 2. Kaplan-Meier plots of progression-free survival according to ECOG(A) and NLR (B).

Univariate analysis performed to predict progression-free survival showed that high NLR (p<0.023), high ECOG performance score (p<0.001), high SII (p<0.037), high neutrophil (p<0.001) were associated with poor PFS (Figure 2). The Multivariate Cox regression model for PFS revealed that ECOG (HR = 1.34, 95% CI, 1.06 - 1.67, p = 0.017) and NLR (HR = 3.39, CI 1.40 - 8.20, p = 0.007) were independent prognostics. The Multivariate Cox regression model for PFS revealed that ECOG (HR = 1.34, 95% CI, 1.06 - 1.67, p = 0.017) and NLR (HR = 3.39, CI 1.40 - 8.20, p = 0.007) were independent prognostics.

Discussion

We investigated the prognostic significance of pretreatment NLR, SII, PNI, and other clinicopathological findings in advanced lung cancer patients who progressed after one line of chemotherapy and received Nivolumab treatment. High NLR, ECOG, high neutrophils, and high SII before Nivolumab treatment were associated with poor progression-free survival, while ECOG, high NLR, high neutrophils, and high leukocyte count were found to be predictors for worse overall survival. Cox regression model showed that ECOG and NLR were worse predictors for PFS and OS.

Before the era of immunotherapy, the expected median survival of advanced-stage NSCLC cancer patients without a targetable driver mutation was about one year [10]. With the use of immunotherapies, there have been significant changes in the survival time of lung cancer patients. In Diem et al.'s study of 52 patients receiving nivolumab for NSCLC cancer, mOS and mPFS were 9.6 and 2.1, respectively. They reported that high NLR, poor ECOG, and smoking history before nivolumab treatment were associated with worse overall survival. In another study conducted in China, Liu J. et al stated that patients with lower SII, NLR, and platelet-to-lymphocyte ratio before treatment had longer PFS and OS in advanced NSCLC receiving nivolumab [11]. In our study, high NLR, neutrophils, and ECOG were found to be predictors for worse PFS and OS, while high SII was associated with poor PFS.

Durable responses obtained with the implementation of immunotherapies, although not in all patients, have led clinicians to choose patients who would benefit from these therapies. PD-L1 has been one of the most frequently studied biomarkers, but it has not provided the desired predictive feature due to method differences in studies, differences in pathological measurements, and high cost [12]. The importance of PD-L1 as a biomarker is less valid for nivolumab, especially [13]. Clinicians need affordable, feasible, reliable markers that can predict the course of the disease. White blood cells or their fractions, which are considered inflammation markers, are hematological parameters reflecting inflammatory conditions. Inflammation in the tumor microenvironment is a well-recognized cause of tumor progression and poor prognosis and its effect has been demonstrated in various tumors [14,15]. These parameters represent the dynamic balance between anti-tumour host immunity and the tumor supporting environment influenced by the inflammatory mediated response. They help clinicians to recognize patients who will benefit from treatment.

Limitation

This study has some limitations. Retrospective and single-center design is the most important limitation of the study. Another limitation is whether hemogram parameters obtained before nivolumab treatment reflect stable clinical status or not. On the other hand, having a larger number of patients compared to other studies in the literature and reflecting real-life data are the strengths of the study.

Conclusion

In conclusion, this study elucidated the prognostic value of NLR, SII, PNI and other clinicopathologic features in advanced non-small cell lung cancer patients treated with Nivolumab. The findings reveal that high NLR, elevated neutrophil counts, and poorer ECOG performance status predict worse progression-free and overall survival. These parameters provide valuable insights into the complex interplay between inflammation, immune response, and tumor progression, potentially guiding the identification of patients who would benefit most from immunotherapy treatment. This study highlights the significance of easily accessible prognostic markers for improved patient stratification.

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Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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